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(57) Abstract

The invention is directed to controlled– or sustained–release compositions for the release of pharmaceuticals or other agents. Essential components in the compositions of the present invention include one or more polymers and tannic acid or tannin. Release of the pharmaceutical or other agent is for a predetermined period of time and at a predetermined concentration. The site of action of the agent is topical, local or systemic. Polymers are cellulosic or proteinaceous.

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Tannic Acid-Polymer Compositions for Controlled Release of Pharmaceutical Agents, Particularly in the Oral Cavity

Background of the Invention

Field of the Invention

The field of the invention is controlled or sustained release compositions for the release of one or more pharmaceuticals or other agents. Essential components in the compositions of the present invention include one or more polymers and tannic acid or tannin. Release of the desired agent can be adjusted to a predetermined period of time and for a predetermined concentration. The site of action of the agent is topical, local or systemic. Polymers are cellulosic or proteinaceous.

Related Art

Controlled-release products are well known in the pharmaceutical field and are used to maintain a desired level of medicament over a desired period of time while increasing patient compliance by reducing the number of administrations necessary to achieve the desired level.

Compositions Comprising Polymers and Tannic Acid or Tannin

Calderon *et al.*, *J. Agr. Food Chem. 16*:479 (1968), compared tannic acid and quebracho tannin coprecipitation with gelatin to form gelatin/tannin precipitates. Calderon disclosed that proteins as different as egg albumin and gelatin readily combine with tannins to form precipitates. Calderon addressed the problem of the formation of precipitates between proteins and tannins in natural beverages such as fruit juice, wines and beer, and further explored the possibility that adding a protein, such as gelatin, to the hazy solution could entrap haze

particles and decrease tannin in the beverage. Calderon was not directed to any use for the precipitates, and did not further characterize them.

U.S. Patent No. 3,255,018 discloses an adhesive chewing gum containing a tannic acid and gelatin complex. This complex is added to make the gum base non-adhesive to the teeth.

U.S. Patent No. 3,679,792 discloses a chewing gum composition having anti-caries activity. The chewing gum contains a gelatin-tannic acid adduct used as an adhesive to counteract the tendency of chewing gum compositions to adhere to teeth, and particularly to certain types of dentures and artificial teeth.

U.S. Patent No. 4,274,410 discloses an intra-vaginal contraceptive and drug-release sponge. The document discloses a collagen slurry and a tanning agent to cross-link the collagen.

U.S. Patent No. 5,223,029 discloses a hardening material for medical and dental use. Essential components include tri-calcium phosphate or tetra-calcium phosphate and a hardening adjuster that may comprise tannin and collagen. The document suggests using decomposed gelatin (water-soluble gelatin or gelatin 21, products of Nitta Gelatin Inc.). Collagen can be used by preparing a solution independent of the tannin solution, by dissolving it in the tannin solution, or by using it in its powdered state. No use, other than a hardener, and no physical characteristics of the tannin-collagen combination is given. Further, the document discloses the use of the complex for the slow release of tannic acid for the formation of a cement and not as a flexible adhesive. Further, there is no suggestion that this complex should be used for drug release or is suitable for this purpose.

Rodu *et al., J. Oral Pathol. 17*:324 (1988), evaluated the *in vitro* virucidal activity of soluble components of a topical film-forming medication, Zilactin™. Zilactin™ is a hydroxypropylcellulose-based film-forming medication. Other active ingredients include tannic acid, salicylic acid and boric acid, which are disclosed as necessary for the unique adherent film-forming properties of the medication.

Rodu *et al., J. Oral Pathol. 17*:564 (1988), discloses a bioadhesive agent, Zilactin™, as a mucosal bioadhesive that is based on hydroxypropylcellulose and is complexed with three organic acids. Zilactin™ is reported to form an adherent and soluble film resulting in significant pain relief and protection of ulcers from irritants for several hours. The medication was made, among other embodiments, with a combination of hydroxypropylcellulose and tannic acid dissolved in SD40 alcohol for comparison testing with the parent compound Zilactin™. The physical properties of this binary complex were not investigated, and no use for this complex for releasing drugs was disclosed or suggested.

U.S. Patent No. 5,081,157 discloses a film-forming composition for topical application of medicaments to body tissues. The film-forming composition includes hydroxypropylcellulose for treating skin mucosal tissue and other moist tissue by forming an adherent film. An esterification agent is an essential component of the film. A weak carboxylic acid such as tannic acid is suggested as the specific esterification agent component. The cellulosic compound is reacted with the weak carboxylic acid to form the film.

Gamiz Gracia, *et al., J. Pharm. Biomed. Anal. 15*:447 (1997) discloses a flow injection analysis method to determine albumin tannate in tablets. Albumin tannate is a compound of tannic acid (tannin) with albumin (50%), used for its astringent properties in the treatment of diarrhea. This document discloses albumin tannate as a drug and not as a drug carrier. No physical properties of this compound are reported.

U.S. Patent No. 4,524,824 discloses a dental cement in which a tannic acid derivative, consisting of a tannic acid-protein combination, is reported. Suggested proteins include albumin and gelatin. Precipitates are formed between the tannic acid and the protein. The precipitates are used for the slow release of tannic acid for the formation of a cement and not to form a flexible adhesive. Moreover, there is no disclosure or suggestion to use such a complex to release a drug. None of the physical characteristics of the complex is provided.

WO 93/10827 discloses coating guidewires using a protein-based coating that has been pretreated by the addition of weak organic acids, for example tannic acid. Suggested proteins include gelatin, collagen and albumin. No physical characteristics are provided for the coating. Furthermore, there is no disclosure or suggestion to release a pharmaceutical from the coating.

Oral Delivery Systems

Oral controlled-release delivery systems should ideally be adaptable so that release rates and profiles can be matched to physiological and chronotherapeutic requirements. The art describes free forms, such as sublingual tablets, troches, and buccals. In addition to non-attached oral sustained or controlled release forms, other forms are designed to adhere to the oral mucosa and deliver an active pharmaceutical agent either directly into the oral mucosa, or into the saliva. Ointments and other sticky adhering compositions also have been used. The active ingredient in all these forms can act locally or systemically.

U.S. Patent No. 4,829,056 describes a buccal tablet consisting of etorphine, at least one monosaccharide, disaccharide or mixture thereof, and a mixture of xanthan gum and locust bean gum in a weight ratio of 3:1 to 1:1, wherein the total weight of the mono- and/or disaccharides relative to the combined weight of xanthan and locust bean gums is in the ratio of 20:1 to 3:1. The buccal tablet is intended to be placed between the gingival surface of the jaw and the buccal mucosa where it gels to produce a soft hydrated tablet which may be retained in position so as to provide release of etorphine for up to two hours. The buccal tablet is said to provide improved bioavailability.

U.S. Patent No. 4,948,580 describes a bioadhesive composition which may be employed as an oral drug delivery system and includes a freeze-dried polymer mixture formed of the copolymer poly(methyl vinyl ether/maleic anhydride) and gelatin dispersed in an ointment base. This composition is said to be useful to

deliver active ingredients such as steroids, antifungal agents, and antibacterial agents, to the oral mucosa.

U.S. Patent No. 4,597,959 describes a cosmetic breath freshener composition in wafer form which is said to have slow release properties. The composition includes a multiplicity of microencapsulated liquid droplets of flavoring material contained in an adhesive base.

U.S. Patent No. 5,077,051 describes bioadhesive microcapsules which comprise xanthan gum, locust bean gum, a bulking agent and an active agent. The microcapsules are said to be useful for delivering buffering agents to the oral cavity for anticarious purposes. The microcapsules are prepared by preparing a hot aqueous solution or suspension of the active agent; adding xanthan gum, locust bean gum and a bulking agent to form a viscous solution; and then (a) cooling and then drying the viscous solution to obtain a solid material which is then formed into microcapsules, or (b) spray-drying the viscous solution to form the microcapsules.

U.S. Patent No. 4,915,948 describes a tablet which is said to have improved adhesion to mucous membranes. The tablet includes a water soluble biopolymer selected from xanthan gum, a pectin and mixtures thereof, and a solid polyol having a solubility at room temperature in water greater than about 20g/100g solution.

U.S. Patent Nos. 4,994,276, 5,128,143, and 5,135,757, describe a controlled release excipient comprised of synergistic heterodisperse polysaccharides (e.g., a heteropolysaccharide, such as xanthan gum in combination with a polysaccharide gum capable of cross-linking with the heteropolysaccharide, such as locust bean gum) that is capable of processing into oral solid dosage forms using either direct compression, following addition of drug and lubricant powder, conventional wet granulation, or a combination of the two. Release of the medicament from the formulations is reported to proceed according to zero-order or first-order mechanisms.

U.S. Patent No. 4,059,686 describes a pharmaceutical preparation for oral cavity administration characterized by being a mixture of a pharmacologically active agent, a pharmaceutical carrier, and sodium polyacrylate in conventional dosage form. It adheres strongly to a local site and dissolves gradually over a prolonged period of time, releasing appropriate amounts of the active agent. The preparation is designed to adhere to mucosal membranes.

U.S. Patent No. 4,876,092 describes a sheet-shaped adhesive preparation comprising an adhesive layer containing, as essential components, a carboxyvinyl polymer, a water-insoluble methacrylic copolymer, a polyhydric alcohol, and a pharmaceutically active agent, and a water-impermeable and water-insoluble carrier layer containing, as essential components, a pharmaceutically active, water-insoluble, film-forming high molecular weight compound and a plasticizer, which can adhere within the oral cavity over a period of time and release an active agent. The preparation is designed to be adhered to the mucous membrane.

U.S. Patent No. 3,972,995 describes a dosage form for buccal administration of a drug, and which is directly applicable to the interior surfaces of the mouth. The dosage form is comprised of a support member which is water-insoluble, waterproof and flexible, a moisture-activated adhesive precursor applied to one surface of the support member, and an active ingredient applied to the central portion of the support member, either directly or dispersed in a matrix. The dosage form is applied directly to the interior surface of the mouth. Contact with saliva activates the adhesive and causes the support member to adhere to the interior surface of the mouth, thereby exposing the active ingredient to a limited area of the oral mucosa while isolating the active ingredient from the remainder of the oral environment.

U.S. Patent No. 5,330,761 describes a controlled release bioadhesive tablet which includes a locally active agent, a heterodisperse gum matrix, and a pharmaceutically acceptable diluent. The final product adheres to mucous membranes and releases the locally active agent over a desired period of time.

Nagai, T., *et al.* (*J. Cont. Rel.* 6:353 (1987)) describes a sustained-release tablet capable of sticking tightly to human gingiva and not the cheek mucosa. Further described is a self-administered plaster with a water-impermeable backing layer (film).

U.S. Patent No. 4,772,470 discloses an oral bandage comprising a soft adhesive film comprising a mixture of polycarboxylic acid and/or a polycarboxylic acid anhydride and a vinyl acetate polymer in a compatible state, and an oral preparation comprising such an oral bandage having incorporated therein a topical drug. The oral bandage or preparation is reported to exhibit strong adhesion of long duration when applied to the oral mucosa or teeth. This patent purports to teach a composition for topical administration of pharmaceutically active agents. It is drawn primarily to the use of anesthetic compositions, but may comprise other agents as well. The composition comprises the active agent in a pharmaceutically acceptable solvent, and in an admixture also includes a bioadhesive.

U.S. Patent No. 4,900,554 describes an adhesive device for application to body tissue having an adhesive layer and a backing layer positioned over one side of the adhesive layer. The adhesive layer includes one or more acrylic acid polymers having adhesive properties upon dissolution or swelling in water and at least one water-insoluble cellulose derivative. The backing layer is water-insoluble or sparingly water-soluble. This patent discloses a composition comprising the active agent in an admixture that also includes a bioadhesive. Further, it includes a backing layer so that the adhesive does not adhere to adjacent areas.

U.S. Patent No. 5,446,070 relates to compositions and methods for topical administration of pharmaceutically active compounds and specifically to anesthetic compounds for topical administration. The invention is a flexible bioadhesive composition for topical administration. The invention is a flexible bioadhesive composition for topical application comprising a pharmaceutically active agent, a solvent and a plasticizer, in admixture with a polysaccharide bioadhesive carrier, wherein the composition is substantially free of water, substantially water-

insoluble, and wherein the pharmaceutically active agent is present in a non-crystallized form. The patent discloses that an exceptionally high loading of anesthetic agents can be added to a carrier without loss of the adhesive properties, so that more rapid delivery of an anesthetic agent to a tissue without substantial crystallization of the agent can occur. The document discloses the use of the composition for topical administration to hard tissue such as teeth.

European Patent Application 223 245 discloses a curable composition containing methacrylate monomers and a polymerization initiator for application to teeth and having the property of *in situ* polymerization to form a hardened filler. The document discloses the use of such filler in combination with an active agent, thereby releasing the active agent from the hardened filler.

Furthermore, each of the above-cited references further discuss sustained-release compositions, many of which can be used to release a pharmaceutically active agent in the oral cavity.

Several problems are associated with controlled-release or sustained-release formulations in the oral cavity.

A major problem is providing prolonged release at effective concentrations. For example, fungal infections beginning in the mouth and then entering other parts of the body are life-threatening to immuno-compromised patients. It is thus desirable to release antifungal agents on an ongoing basis. However, it is very difficult to achieve.

Buccal tablets and sublingual tablets are pharmaceutical preparations primarily intended for systemic effect. These tablets are placed between the cheek and gingival or under the tongue and allowed to dissolve slowly. The drugs absorbed through the oral mucous membrane enter directly, not through the portal circulation but through the systemic circulation. An advantage of these tablets is in the efficient absorption of the drug, because the drug is not decomposed by the liver. However, if the disintegration and dissolution of the tablet are too rapid, the object of this method of administration is not achieved.

A problem with these sustained-release devices involves the area of comfort. Patients often reject these oral sustained-release devices because they have a "foreign" feeling. As a result, these devices are often dislodged by the patient.

Recently, a tablet for stomatitis has been developed which is applicable directly to the affected region. But this preparation is also hard and has a certain thickness, and persons using it are aware of its presence. Accordingly, the tablet may be dislodged with the tongue and swallowed during eating and drinking. Therefore, it is difficult to retain within the oral cavity for a long time.

Moreover, the known preparations are usually composed of components which are soluble or disintegrable within the mouth. Thus, the pharmaceutically active agents contained in the preparations are mostly swallowed without being absorbed through the mucous membrane in the oral cavity. Thus, these preparations are not completely satisfactory as a sustained- or controlled-release preparation for the oral cavity.

In order to retard disintegration of the above said preparations, the following trials have been made without successful results as a preparation for oral cavity administration:

1. to add larger amounts of a binder, without employing a disintegrant, such as starch;

2. to add a large amount of hydrophobic lubricant, such as magnesium stearate;

3. to coat the tablet with a water-repellent substance such as wax or paraffin.

Ointments are not satisfactory for oral cavity administration because of insufficient adhesion and rather high solubility.

Mucosal patches, which demonstrate good adhesion for extended periods of time, cause adverse reactions like mucosal itching and irritation at the patch sites or even necrosis in severe cases. (*Contact-Dermatitis 25*(4):230-6 (1991); *Maturitas 13*(2):151-4 (1991).) In addition to health complications, the side

effects profile of a product can lead to added therapeutic costs by requiring treatment by physicians or visits to emergency rooms.

Another problem is localized release to teeth. That is, the application of agents that are designed to be delivered to teeth, for example, tooth whiteners and desensitizing agents, are for the most part wasted because delivery is to the whole oral cavity and not local to the tooth.

Another problem is the difficulty of application of sustained release devices for the oral cavity.

A particular problem involves the difficulty of obtaining prolonged release of highly soluble drugs when the delivery system is in an aqueous environment such as the oral cavity. Hydrogel systems release the drug too quickly. Erosive systems, for example systems using the polymer Eudragit™, also result in release that is undesirably rapid.

Accordingly, there is a need for an oral controlled-release pharmaceutical delivery device with the following characteristics. Release can be sustained at desired concentrations for a desired period of time, and particularly for highly soluble drugs when the delivery system is in an aqueous environment such as the oral cavity. Necrosis is avoided. Release can be localized to teeth. Application is easy and uncomplicated. Patient comfort is provided. The device does not impart a "foreign" feeling to the oral cavity. The device facilitates buccal absorption, resulting in rapid systemic delivery of the released agent. The device can also provide localized treatment of the oral mucosa.

Summary of the Invention

The invention is broadly directed to a liquid composition comprising a polymer and tannic acid or tannin, which composition either dries to form a solid composition capable of controlled release of a pharmaceutical, or forms a precipitate that is capable of being dried to form a solid composition capable of controlled release of a pharmaceutical.

In highly preferred embodiments, the invention is directed to a liquid composition comprising a polymer and tannic acid or tannin, where the liquid composition dries to form an adhesive solid composition capable of controlled release of a pharmaceutical or forms a precipitate that can dry to form an adhesive solid composition capable of controlled release of a pharmaceutical.

The invention further encompasses liquid compositions comprising a polymer and tannic acid or tannin and a pharmaceutical, where the liquid composition dries to form a solid composition capable of controlled release of the pharmaceutical agent or forms a precipitate that is capable of being dried to form a solid composition capable of controlled release of the pharmaceutical.

In highly preferred embodiments, the invention is directed to a liquid composition comprising a polymer and tannic acid or tannin and a pharmaceutical, where the liquid composition dries to form an adhesive solid composition capable of controlled release of the pharmaceutical, or forms a precipitate that dries to form an adhesive solid composition capable of controlled release of the pharmaceutical.

The invention further encompasses a liquid composition comprising a polymer and tannic acid or tannin and a pharmaceutical, wherein the pharmaceutical agent is entrapped in liposomes or microcapsules, microspheres, nanocapsules or nanospheres and where the liquid composition dries to form a solid composition capable of controlled release of the pharmaceutical agent or forms a precipitate that is capable of being dried to form a solid composition capable of controlled release of the pharmaceutical.

In highly preferred embodiments, the invention is directed to a liquid composition comprising a polymer and tannic acid or tannin and a pharmaceutical wherein the pharmaceutical agent is entrapped in liposomes or microcapsules, microspheres, nanocapsules or nanospheres and where the liquid composition dries to form an adhesive solid composition capable of controlled release of the pharmaceutical agent or forms a precipitate that is capable of being dried to form an adhesive solid composition capable of controlled release of the pharmaceutical.

The invention naturally encompasses solid compositions comprising a polymer, tannic acid or tannin, and a pharmaceutical, where the solid composition is capable of controlled release of the pharmaceutical.

In preferred embodiments, the invention is directed to a solid adhesive composition comprising a polymer, tannic acid or tannin, and a pharmaceutical, where the solid composition is capable of controlled release of the pharmaceutical.

In preferred embodiments, the polymer is a protein. Preferred proteins include, but are not limited to, gelatin, hydrolyzed gelatin, albumin and collagen.

In alternative embodiments, the polymer is a cellulosic polymer. Preferred polymers include, but are not limited to, hydroxyethylcellulose, hydroxypropylcellulose, and hydroxypropylmethylcellulose.

The invention is also directed to methods of making each of the compositions disclosed herein.

The invention is also directed to the use of the solid compositions in the treatment of various conditions, or in uses where controlled release of an agent is desirable.

In preferred embodiments, the invention is directed to a composition for sustained release of a pharmaceutical in the oral cavity.

In a highly preferred form, the invention is in the form of a pharmaceutical oral patch that can be attached to the surface of a tooth or other hard dental structure where it can release an agent for topical, systemic, or local treatment.

Brief Description of the Figures

Figure 1: *In vitro* release of nicotine from patches containing nicotine entrapped in liposomes compared to patches containing nicotine not entrapped in liposomes. Figure 1 shows the average release of nicotine from Patches # 285-23A (I, II), 285-23B (III, IV), 285-28(V) containing centrifuged liposomes Type MLV, and comparison to nicotine release from non-liposomal nicotine Patches #

49A00 (VI,VIII). The filled circle is I-II; the filled square is III-IV; the open triangle is V, and the filled triangle is VI-VIII.

Figure 2: *In vivo* release of nicotine from patches containing nicotine entrapped in liposomes compared to patches containing nicotine not entrapped in liposomes. Figure 2 shows release of nicotine from patch # 285-28 containing centrifuged liposomes Type MLV compared to nicotine release from non-liposomal Patch #158-64. The solid circle is #285-28 and the solid box is #158-64.

Figure 3: *In vitro* release of flurbiprofen from patch.

Detailed Description of the Preferred Embodiments

The invention is broadly directed to a liquid composition comprising a polymer and tannic acid or tannin, which composition either dries to form a solid composition capable of controlled release of a pharmaceutical, or forms a precipitate that is capable of being dried to form a solid composition capable of controlled release of a pharmaceutical.

In preferred embodiments, the polymer is a protein. Preferred proteins include, but are not limited to, gelatin, hydrolyzed gelatin, albumin and collagen.

In alternative embodiments, the polymer is a cellulosic polymer. Preferred polymers include, but are not limited to, hydroxyethylcellulose, hydroxypropylcellulose, and hydroxypropylmethylcellulose.

In preferred embodiments of the invention, the liquid composition comprises a mixture of the polymer and tannic acid or tannin.

The minimal essential components of the liquid composition can be a polymer and tannic acid or tannin. It is understood, however, that the liquid composition may contain more than one polymer. Thus, the composition can encompass more than one protein, more than one cellulosic polymer, and combinations of the two.

Thus, the composition can consist essentially of any of the proteins or cellulosic polymers disclosed herein, as well as other appropriate proteins and cellulosic polymers, and tannic acid or tannin.

Optional components include plasticizers, such as glycerol, polyethylene glycols, and citrate esters, glycerol being a particularly preferred plasticizer when the polymer is a hydrolyzed gelatin.

However, glycerol may also be used as a plasticizer with other proteins described herein or in general embodiments in which a protein is used in combination with tannic acid or tannin.

Emulsifiers may also be added, optionally.

In highly preferred embodiments, the invention is directed to a liquid composition comprising a polymer and tannic acid or tannin, where the liquid composition dries to form an adhesive solid composition capable of controlled release of a pharmaceutical or forms a precipitate that can dry to form an adhesive solid composition capable of controlled release of a pharmaceutical.

In preferred embodiments, the polymer is a protein. Preferred proteins include, but are not limited to, gelatin, hydrolyzed gelatin, collagen and albumin.

In alternative embodiments, the polymer is a cellulosic polymer. Preferred cellulosic polymers include, but are not limited to, hydroxyethylcellulose, hydroxypropylcellulose, and hydroxypropylmethylcellulose.

In preferred embodiments, the liquid composition comprises a mixture of the polymer and tannic acid or tannin.

The minimal essential components in the liquid composition can be the polymer and tannic acid or tannin. It is understood, however, that the liquid composition may contain more than one polymer. Thus, the composition encompasses more than one protein, more than one cellulosic polymer, and combinations of the two.

Thus, the composition can consist essentially of any of the proteins or cellulosic polymers disclosed herein, as well as other appropriate proteins and cellulosic polymers, and tannic acid or tannin.

Other components are optionally included. These include plasticizers, such as glycerol, polyethylene glycols and citrate esters, with glycerol being the particularly preferred plasticizer when the polymer is a hydrolyzed gelatin.

Emulsifiers may also be added optionally.

The invention further encompasses liquid compositions comprising a polymer and tannic acid and tannin and a pharmaceutical, where the liquid composition dries to form a solid composition capable of controlled release of the pharmaceutical or forms a precipitate that is capable of being dried to form a solid composition capable of controlled release of the pharmaceutical.

In preferred embodiments, the polymer is a protein. Preferred proteins include, but are not limited to, gelatin, hydrolyzed gelatin, collagen and albumin.

In alternative embodiments, the polymer is a cellulosic polymer and tannic acid or tannin and a pharmaceutical. Preferred cellulosic polymers include, but are not limited to, hydroxyethylcellulose, hydroxypropylcellulose, and hydroxypropylmethylcellulose.

In preferred embodiments, the liquid composition comprises a mixture of the polymer, tannic acid or tannin, and a pharmaceutical.

The minimal essential components of the liquid composition can be, therefore, a polymer, tannic acid or tannin, and the pharmaceutical. However, it is to be understood that more than one polymer or type of polymer can be included. That is, more than one protein, more than one cellulosic polymer, and combinations of the two, are encompassed.

Thus, the composition can consist essentially of any of the proteins or cellulosic polymers disclosed herein, as well as other appropriate proteins and cellulosic polymers, and tannic acid or tannin, and the pharmaceutical.

Optional agents include plasticizers such as glycerol, polyethylene glycols and citrate esters, glycerol being the particularly preferred plasticizer when the polymer is a protein, and particularly hydrolyzed gelatin.

Emulsifiers may also be added optionally.

In highly preferred embodiments, the invention is directed to a liquid composition comprising a polymer and tannic acid or tannin and a pharmaceutical, where the liquid composition dries to form an adhesive solid composition capable of controlled release of the pharmaceutical, or forms a precipitate that dries to form an adhesive solid composition capable of controlled release of the pharmaceutical.

In preferred embodiments, the polymer is a protein. Preferred proteins include, but are not limited to, gelatin, hydrolyzed gelatin, collagen and albumin.

Alternatively, the polymer is a cellulosic polymer. Preferred cellulosic polymers include, but are not limited to, hydroxyethylcellulose, hydroxypropylcellulose, and hydroxypropylmethylcellulose.

In preferred embodiments, the liquid composition comprises a mixture of the polymer and tannic acid or tannin and the pharmaceutical.

The minimal essential components for forming the adhesive solid composition can be the polymer, tannic acid or tannin, and a pharmaceutical. It is understood, however, that the liquid composition may contain more than one polymer or type of polymer. Thus, the composition encompasses mixtures of various proteins, cellulosic polymers, and combinations of the two.

Thus, the composition can consist essentially of any of the proteins or cellulosic polymers disclosed herein, as well as other appropriate proteins and cellulosic polymers, and tannic acid or tannin, and the pharmaceutical.

Optional components include plasticizers such as glycerol, polyethylene glycols and citrate esters, glycerol being the particularly preferred plasticizer when the polymer is hydrolyzed gelatin.

Emulsifiers may also be added optionally.

The invention further encompasses liquid compositions comprising a polymer and tannic acid or tannin and a pharmaceutical, wherein the pharmaceutical agent is entrapped in liposomes or microcapsules, microspheres, nanocapsules or nanospheres and where the liquid composition dries to form a solid composition capable of controlled release of the pharmaceutical agent or

forms a precipitate that is capable of being dried to form a solid composition capable of controlled release of the pharmaceutical.

Also for this aspect of the invention in which the pharmaceutical agent is entrapped in liposomes or microcapsules, microspheres, nanocapsules or nanospheres, in preferred embodiments, the polymer is a protein. Preferred proteins include, but are not limited to, gelatin, hydrolyzed gelatin, collagen, and albumin.

The liposome may be a multilamellar vesicle or unilamellar vesicle. Liposomes comprise phospholipids and/or sphingolipids and optionally lipids such as cholesterol and phosphatidic acid and antioxidants. Preferred phospholipids are soybean lecithin, egg lecithin, soybean phosphatidylcholine, egg phosphatidylcholine, synthetic phosphatidylcholine, phosphatidylserine, phosphatidylinositol, phosphatidylglycerol, phosphatidylethanolamine, alone or in mixtures. A preferred sphingolipid is sphingomyelin. Highly preferred liposomes comprise phosphatidylcholine, phosphatidylethanolamine, cholesterol and an antioxidant.

The microcapsule, microsphere, nanocapsule or nanosphere comprises polymers and optionally plasticizers and emulsifiers. The preferred polymers comprising these microcapsules, microspheres, nanocapsules or nanospheres are polyalkyl methacrylate such as polymethylmethacrylate, polyalkylcyanoacrylates such as polymethylcyanomethacrylate, polyesters such as polylactic acid and polylactic/glycolic acid copolymers, cellulose derivatives such as ethylcellulose and cellulose acetate and proteins such as albumin, gelatin, and hydrolyzed gelatin, and polysaccharides such as sodium alginate, pectin, chitosan, guar gum, and xanthan gum.

In alternate embodiments of the liquid composition of the invention the polymer is a cellulosic polymer. Preferred cellulosic polymers include, but are not limited to, hydroxyethylcellulose, hydroxypropylcellulose, and hydroxypropylmethylcellulose.

In preferred such embodiments, the liquid composition comprises a mixture of the polymer, tannic acid or tannin, and a pharmaceutical entrapped in liposomes or microcapsules, microspheres, nanocapsules or nanospheres.

The minimal essential components of the liquid composition can be, therefore, a polymer, tannic acid or tannin, and the pharmaceutical entrapped in a liposome or microcapsule, microsphere, nanocapsule or nanosphere. However, it is to be understood that more than one polymer or type of polymer can be included. That is, more than one protein, more than one cellulosic polymer, and combinations of the two, are encompassed. It is further understood that more than one type of liposome or microcapsule, microsphere, nanocapsule or nanosphere or combination of any of them, are also encompassed.

Thus the composition can consist essentially of any of the proteins or cellulosic polymers disclosed herein, as well as other appropriate proteins and cellulosic polymers, and tannic acid or tannin, and the pharmaceutical entrapped in any of the liposomes or microcapsules, microspheres, nanocapsules or nanospheres, or combination of liposomes or microcapsules, microspheres, nanocapsules or nanospheres as disclosed herein.

Optional agents include plasticizers such as glycerol, polyethylene glycols, and citrate esters, glycerol being the particularly preferred plasticizer when the polymer is a protein, and particularly hydrolyzed gelatin.

Emulsifiers may also be added optionally.

In highly preferred embodiments, also for this additional aspect of the invention in which the pharmaceutical agent is entrapped in liposomes or microcapsules, microspheres, nanocapsules or nanospheres, the invention is directed to liquid compositions comprising a polymer and tannic acid or tannin and a pharmaceutical wherein the pharmaceutical agent is entrapped in liposomes or microcapsules, microspheres, nanocapsules or nanospheres and where the liquid composition dries to form an adhesive solid composition capable of controlled release of the pharmaceutical agent or forms a precipitate that is capable of being

dried to form an adhesive solid composition capable of controlled release of the pharmaceutical.

In preferred embodiments, the polymer is a protein. Preferred proteins include, but are not limited to, gelatin, hydrolyzed gelatin, collagen, and albumin.

The liposomes may be a multilamellar vesicle or a unilamellar vesicle. Liposomes comprise phospholipids and/or sphingolipids and optionally lipids such as cholesterol and phosphatidic acid and antioxidants. Preferred phospholipids are soybean lecithin, egg lccithin, soybean phosphatidylcholine, egg phosphatidylcholine, synthetic phosphatidylcholine, phosphatidylserine, phosphatidylinositol, phosphatidylglycerol, phosphatidylethanolamine, alone or in mixtures. A preferred sphingolipid is sphingomyelin. Highly preferred liposomes comprise phosphatidylcholine, phosphatidylethanolamine, cholesterol and an antioxidant.

The microcapsule, microsphere, nanocapsule or nanosphere comprises polymers and optionally plasticizers and emulsifiers. The preferred polymers comprising these or microcapsules, microspheres, nanocapsules or nanospheres are polyalkyl methacrylate such as polymethylmethacrylate, polyalkylcyanoacrylates such as polymethylcyanomethacrylate, polyesters such as polylactic acid and polylactic/glycolic acid copolymers, cellulose derivatives such as ethylcellulose and cellulose acetate and proteins such as albumin, gelatin, and hydrolyzed gelatin, and polysaccharides such as sodium alginate, pectin, chitosan, guar gum, and xanthan gum.

In alternate embodiments of the liquid composition of the invention the polymer is a cellulosic polymer. Preferred cellulosic polymers include, but are not limited to, hydroxyethylcellulose, hydroxypropylcellulose, and hydroxypropylmethylcellulose.

In such preferred embodiments, the liquid composition comprises a mixture of the polymer, tannic acid or tannin, and a pharmaceutical entrapped in liposomes or microcapsules, microspheres, nanocapsules or nanospheres.

The minimal essential components of the liquid composition can be, therefore, a polymer, tannic acid or tannin, and the pharmaceutical entrapped in a liposome or microcapsule, microsphere, nanocapsule or nanosphere. However, it is to be understood that more than one polymer or type of polymer can be included. That is, more than one protein, more than one cellulosic polymer, and combinations of any of them, are encompassed. It is further understood that more than one type of liposome or microcapsule, microsphere, nanocapsule or nanosphere or combination of the two, are also encompassed.

Thus the composition can consist essentially of any of the proteins or cellulosic polymers disclosed herein, as well as other appropriate proteins and cellulosic polymers, and tannic acid or tannin, and the pharmaceutical entrapped in any of the liposomes or microcapsules, microspheres, nanocapsules or nanospheres, or combination of liposomes or microcapsules, microspheres, nanocapsules or nanospheres as disclosed herein.

Optional agents include plasticizers such as glycerol, polyethylene glycols, and citrate esters, glycerol being the particularly preferred plasticizer when the polymer is a protein, and particularly hydrolyzed gelatin.

Emulsifiers may also be added optionally.

The invention naturally encompasses solid compositions comprising a polymer, tannic acid or tannin, and a pharmaceutical, where the solid composition is capable of controlled release of the pharmaceutical.

In preferred embodiments, the polymer is a protein. Preferred proteins include, but are not limited to, gelatin, hydrolyzed gelatin, albumin and collagen.

Alternatively, the polymer is a cellulosic polymer. Preferred polymers include, but are not limited to, hydroxyethylcellulose, hydroxypropylcellulose, and hydroxypropylmethylcellulose.

Since the liquid composition can comprise a mixture of the polymer, tannic acid or tannin and the pharmaceutical, the solid composition accordingly comprises a mixture of a polymer, tannic acid or tannin, and a pharmaceutical.

Thus, the pharmaceutical is dispersed or embedded in the dried matrix of the polymer-tannic acid/tannin.

The minimal essential components in the solid composition can include the polymer, tannic acid or tannin, and a pharmaceutical. It is understood, however, that the solid composition may contain more than one suitable polymer. Thus, the composition encompasses more than one protein, more than one cellulosic polymer, and combinations of the two.

Thus, the solid composition can consist essentially of any of the proteins or cellulosic polymers disclosed herein, as well as other appropriate proteins and cellulosic polymers, and tannic acid or tannin and the pharmaceutical.

When appropriate, the solid composition of this invention may be coated with a suitable pharmaceutical coating.

In preferred embodiments, the invention is directed to a solid adhesive composition comprising a polymer, tannic acid or tannin, and a pharmaceutical, where the solid composition is capable of controlled release of the pharmaceutical.

In preferred embodiments, the polymer is a protein. Preferred proteins include, but are not limited to, gelatin, hydrolyzed gelatin, albumin and collagen.

Alternatively, the polymer is a cellulosic polymer. Preferred cellulosic polymers include, but are not limited to, hydroxyethylcellulose, hydroxypropylcellulose, and hydroxypropylmethylcellulose.

The solid adhesive composition comprises a mixture of a polymer, tannic acid or tannin and a pharmaceutical.

Thus, the pharmaceutical is dispersed or embedded in the dried adhesive matrix of the polymer-tannic acid/tannin.

The minimal essential components in the solid adhesive composition can be the polymer, tannic acid or tannin, and the pharmaceutical. It is understood, however, that the solid composition may contain more than one polymer. Thus, the composition encompasses more than one protein, more than one cellulosic polymer, and combinations of the two.

Accordingly, the composition can consist essentially of any of the proteins or cellulosic polymers disclosed herein, combinations thereof, as well as other appropriate polymers, and tannic acid or tannin, and a pharmaceutical.

The solid compositions described herein encompass biodegradable formulations.

Although the above description relates specifically to the release of pharmaceuticals, it is to be understood that other agents can be released from the solid compositions described herein. Examples of such agents include, but are not limited to, cosmetics, vitamins, minerals, flavorants, colorants, toxins such as pesticides, odorants, and the like.

For controlling the release of a pharmaceutical or other agent from the solid compositions disclosed herein, the agent can be entrapped in the polymer:tannic acid matrix. The extent of such entrapment, and thereby the extent of sustained release, is controlled by the choice of polymer.

The solvents used to prepare the polymer-tannic complex can be useful as release-adjusting agents, since they can strongly affect the release rate, as shown in the examples herein.

An outer polymer matrix as shown in the examples herein, is a form of release-adjusting agent because it contributes to controlling the release of the drug. It can be formulated with or without its own release-adjusting agents, to retard release from the inner matrix by varying amounts.

Release of the pharmaceutical can also be controlled by the addition of pH-adjusting agents, release-adjusting agents, solubility-adjusting agents, and combinations thereof, to the solution or suspension of the polymer being added to the dried precipitate.

The invention is also directed to methods of making each of the compositions disclosed herein.

In its broadest embodiment, the polymer and tannic acid or tannin are mixed in a solvent, and the mixture is then dried to form the solid composition.

Alternatively, the polymer may be first dissolved in a solvent and the tannic acid or tannin separately dissolved in a solvent prior to mixing.

The polymer may or may not form a precipitate when mixed with the tannic acid or tannin. In embodiments in which the tannic acid or tannin forms a precipitate with the polymer, the composition is made as follows:

(1) the polymer is dissolved in a solvent,

(2) tannic acid or tannin is added in a solvent,

(3) a precipitate is allowed to form,

(4) the precipitate is dried to form the solid composition.

A pharmaceutical(s) can be added to the polymer solution or the tannic acid solution. When added to a polymer solution which will form a precipitate, the pharmaceutical is then mixed in the precipitate that is formed, so that when the precipitate is dried the pharmaceutical is embedded or dispersed in the solid composition formed from the precipitate.

In alternative embodiments, however, the solid composition can be formed as in steps 1-4 and then one or more pharmaceuticals can be added to this precipitate that is further processed for controlled release of the pharmaceutical(s) from the dried precipitate. The drug can be added to the dried precipitate in solution and then subsequently dried or can be mixed in powdered form with the precipitate. This can then be pressed or otherwise formed together according to methods well known in the art.

Preferred solvents for the polymer include, but are not limited to, water, ethanol, and mixtures of water and ethanol, isopropanol, mixtures of water and isopropanol, *n*-propanol, and mixtures of water and *n*-propanol.

Preferred solvents for the tannic acid or tannin include, but are not limited to, water, ethanol, and mixtures of water and ethanol, isopropanol, mixtures of water and isopropanol, *n*-propanol, and mixtures of water and *n*-propanol.

When the polymer is a protein, preferred solvents include, but are not limited to, water, ethanol, and mixtures of water and ethanol, isopropanol,

mixtures of water and isopropanol, *n*-propanol, and mixtures of water and *n*-propanol.

When the polymer is a cellulosic polymer, preferred solvents include, but are not limited to, water, ethanol, and mixtures of water and ethanol, isopropanol, mixtures of water and isopropanol, *n*-propanol, and mixtures of water and *n*-propanol.

When the polymer and tannic acid are dissolved in the same solvent, preferred solvents include, but are not limited to, water, ethanol, and mixtures of water and ethanol, isopropanol, mixtures of water and isopropanol, *n*-propanol, and mixtures of water and *n*-propanol.

In alternative embodiments, the dried precipitate disclosed above is ground into a powder, and the powder is then mixed with a further polymer in a solvent, and this mixture is then dried to form the final solid composition. This second polymer thus forms an outer matrix over the complex.

Preferred polymers for mixing with the polymer-tannic acid/tannin precipitate include any polymer that physically binds the powder together, allowing the powder to adhere to the tooth as a mass. The polymer needs to be flexible, and therefore, a plasticizer is essential. The polymer should be degradable and/or allow saliva to diffuse through it to allow for drug release from the powder. The polymer should be either soluble or dispersible in a solvent in which the powder is insoluble, so that the powder will not re-dissolve when the polymer is added.

This second polymer can optionally be formulated with release-adjusting agents, pH-adjusting agents, emulsifiers, and solubility-adjusting agents.

The preferred second polymer is a polyacrylate polymer, and particularly a Eudragit™ polymer.

Preferred polymers that can be used as a second polymer when the first polymer is a protein or a cellulosic polymer include, but are not limited to, Eudragit™ L-100, Eudragit™ L 30D-55, Eudragit™ S-100, Eudragit™ NE-100, Eudragit™ NE-30, Eudragit™ RL, Eudragit™ RS, hydroxypropylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose, pectin, calcium pectinate,

alginic acid, calcium alginate, cellulose acetate phthalate, carbopol, guar gum, gum tragacanth, gum acacia, other vegetable gums, and chitosan.

The second polymer serves as a matrix for the tannic-polymer-complex powder (precipitate). It binds the powder together for ease of application and control of dosage. That is, a premeasured amount of the pharmaceutical agent(s) can be applied in one single application, rather than in repeated applications (as in a varnish coated onto teeth, for example).

It further can help control the rate of releasing the drug by controlling or attenuating the ability of the saliva to interact with the precipitate. The degradation of the polymer and permeability with saliva allow for the release of the powder into the saliva and thereby for the release of the pharmaceutical.

In preferred embodiments, the composition is made as follows: (1) protein and a pharmaceutical are dissolved in a solvent comprising ethanol and water; (2) tannic acid or tannin is added in a solvent comprising ethanol and water; (3) a precipitate is allowed to form; (4) the precipitate is dried to form the solid composition.

In highly preferred embodiments, the first four steps above are performed but the following additional steps are then performed: (5) the dried precipitate is ground into a powder; (6) the powder is mixed with a Eudragit™ polymer and a plasticizer in a solvent comprising ethanol and water or as a latex suspension in water; (7) the mixture is dried.

In highly-preferred embodiments of the invention, the protein is hydrolyzed gelatin and the second polymer is Eudragit™ L-100.

Preferred pharmaceuticals include, but are not limited to, nicotine, nicotine salts, nicotine polymer complexes, lidocaine, piroxicam, flurbiprofen, dihydroergotamine mesylate, ergotamine tartarate, sumaptriptan succinate, isosorbide dinitrate, isosorbide mononitrate, nifedipine, ondansetron hydrochloride, and peptide drugs. Highly or significantly water-soluble pharmaceuticals are particularly suited for release from embodiments in which a

protein-tannic acid/tannin precipitate has been formed. Embodiments including a second polymer are particularly suitable for releasing such pharmaceuticals.

In certain embodiments of the invention, the same or a different pharmaceutical can be added in the second polymer solution and be released therefrom (when solidified).

The invention is also directed to the use of the solid compositions in the treatment of various conditions. The compositions can also be used as a powder or microcapsule in a capsule for oral delivery to the gastrointestinal tract, compressed into tablets alone or with typical excipients for oral delivery to the gastrointestinal tract, as a lozenge for local delivery to the oral cavity or for delivery to the gastrointestinal tract, a suppository for rectal delivery, a vaginal tablet or suppository, or as an ointment for topical use.

Accordingly, depending on the use of the compositions, the physical form of the composition can be adjusted. For example, the compositions may be used as a film, nanoparticle, microparticle or bead. The compositions could also be used as a powder or microcapsules in a capsule, compressed into tablets alone or with typical excipients, as a lozenge, suppository, vaginal tablet or suppository, or as an ointment. When appropriate, the composition of this invention may be coated with a suitable pharmaceutical coating.

In preferred embodiments, the invention is directed to a composition for sustained release of a pharmaceutical in the oral cavity. In a highly preferred form, the invention is in the form of a pharmaceutical oral patch that can be attached to the surface of a tooth, denture, or other hard dental structure.

The method provides for buccal absorption of an active agent resulting in rapid systemic delivery of desired amounts of agent for a desired period of time.

The method also provides for the delivery of an active agent confined to a tooth area and avoiding release elsewhere in the oral cavity.

The method also allows for localized treatment of affected sites in the oral cavity or throat area.

The invention also provides a patient with the compositions described herein by adhesively adhering the solid, sustained-release composition to the hard surface of the patient's mouth, for example, teeth or dentures.

As a pharmaceutical oral patch, the solid composition can be modified into any shape and size, depending on the purposes of drug release. Thus, if large amounts of a drug are to be released, in addition to increasing the concentration of drug, in the sustained-release composition, the solid form can be larger in size and/or greater in thickness.

The important consideration for shape and size is that the patch does not confer unusual sensation to the patient when applied, and can effectively release the desired pharmaceutically active agent at the desired levels and for the desired duration of time. For example, for the rapid release of a small amount of drug, a thin layer, in which the drug is dispersed, may be required.

The following considerations are important in choosing the site of application: (1) the salivary flow around the site; (2) the accessibility for application; (3) the comfort of the patient.

Patch components are suitable to remain in the oral cavity for prolonged periods of time. In a preferred embodiment, the patch remains in the oral cavity between 6 to 8 hours. However, other embodiments can last for various desired periods of time.

The invention is also directed to a method for making the sustained-release compositions so that the rate of release can be adjusted in the final, solid form.

The invention is also directed to methods for using the compositions of the present invention to release appropriate pharmaceutical agents in the oral cavity. Potentially, any pharmaceutically active agent can be released, although, as mentioned, the preferred agents are those that are soluble or very soluble in water.

In addition, potentially any condition can be treated by means of the release of a pharmaceutical from the patch. These are described in more detail below.

Preferred sites of application include but are not limited to the upper teeth.

The sites of action for the pharmaceutically active agents include the oral mucosa of the mouth, throat, and esophagus *per se*, systemic delivery via the oral mucosa, or localized delivery to one or more teeth.

The amount of active agent included in the final, controlled release product can be determined by one skilled in the art without undue experimentation, and is generally from about 0.1% to about 35% by weight of the final product. The particular amount of the active agent included will, of course, depend upon the particular agent and its intended use.

The present invention can include other locally active agents, such as flavorants and sweeteners. The flavoring agents may be natural or synthetic. The flavoring agent is a common flavorant including wintergreen, peppermint, spearmint, menthol, fruit flavors, vanilla, cinnamon, various spices, or others known in the art. Generally any flavoring or food additive, such as those described in *Chemical Used in Food Processing*, Pub. No. 1274, National Academy of Sciences, pages 63-258, can be used. The amount of flavoring employed is normally a matter of preference subject to such factors as flavor type, individual flavor, and strength desired. Generally, the final product includes from about 0.1% to about 5% weight flavorant.

Sweeteners useful in the present invention include sucrose and aspartame. In general, sweeteners (when present) are included in an amount from about 0.001% to about 5.0% by weight of the final product.

Effective amounts of coloring agents (e.g., titanium dioxide, F.D. & C., and D. & C. dyes; see the Kirk-Othmer *Encyclopedia of Chemical Technology*, vol. 5, pp. 857-884); softeners, stabilizers, binders, odor-controlling agents, and preservatives can also be contained in the patch, as long as they do not impair adhesiveness or impede pharmacological effects.

The term "therapeutically effective amount" is intended to mean the amount of pharmaceutically active agent sufficient to produce the desired effect when released from the dental patch described herein. These amounts are known in the art or may be determined by methods known in the art. The amounts

depend upon the agents chosen and whether the site of action is the tooth *per se*, the oral mucosa (and the region of the oral mucosa), or systemic.

The upper limit on the amount of drug in the composition is determined by the properties of the polymeric matrix and the chemical interaction of the drug with the polymeric matrix.

The amount of active agent in the composition necessary to provide the desired amounts and concentration in the oral cavity can be determined by known methods. Thus, the concentration and the quantity of the agent per unit area of the patch (i.e., per square or cubic millimeter) can be varied independently in order to achieve a desired effect. Higher concentrations of agent contained in a dosage form of decreased thickness will result in an agent with fast onset and short duration. High concentrations of an agent contained in a dosage form of increased thickness (higher milligrams of agent per square or cubic millimeter) will result in potent effect with fast onset and long duration. Low concentrations of the agent in a dosage form of decreased thickness will result in mild effect with longer onset and short duration. Low concentrations of the agent contained in a dosage form of increased thickness will have mild effect with longer onset and longer duration. As shown in the above explanation, the ability to coat thin or thick, enables the practitioner of the invention to vary the dosage of the system as needed for particular anatomical sites of interest and according to the specific drug. The term "onset" is intended to mean the time needed to reach the desired concentration level of the pharmaceutical agent. It is used according to its normal and art-recognized meaning.

The term "duration" as used herein, means the period of time during which the desired concentration of pharmaceutical agent is delivered. This term is used according to its normal and art-recognized meaning.

The term "adhesive" as used herein, means an adhesive which attaches, and preferably strongly attaches, the release layer to teeth or other hard structures in the mouth such as dentures. To qualify as an adhesive, the substance must be capable of maintaining adhesion in the moist or wet environments of the oral

cavity. It can also be "self-adhesive" in that it attaches to the site of interest without the need to reinforce its attachment by way of another adhesive. Thus, the term "adhesive" is used according to its normal and art-recognized meaning.

Adhesion can only be quantified with reference to a specific type of test or usage. It is not in itself a basic physical property, such as the surface free energy or the film thickness, whose measurement can be accomplished by a variety of methods. "Adhesion performance" must therefore be defined and measured in the context of the application of interest. Whether a given adhesive is effective for the oral cavity can be determined by a peel test in artificial saliva.

The strength of adherence can be measured by standard tests for measuring the force, for example in dynes per square centimeter, as disclosed in U.S. Patent No. 4,615,697.

The term "subject" or "patient" is intended to include all mammals, preferably humans.

The term "patch", as used herein, is intended to mean a three-dimensional solid composition that can be adhered to teeth, or other hard structures in the mouth, such as dentures, which can contain a pharmaceutically active agent, and which can release the pharmaceutically active agent in effective amounts, for a desired period of time, from its site of attachment within the oral cavity.

By "pharmaceutically active agent" is intended any chemical or biochemical that can be released from the dental patch to prevent, cure, or ameliorate an undesirable physiological condition (see below). The term "drug" is used interchangeably herein. These terms are used according to their normal and art-recognized meanings.

Although any agent can be used, depending on the purpose of therapy, the following are exemplary:

1. anti-inflammatory, analgesic agents: content 0.1-5%
2. steroidal anti-inflammatory agents: content 0.002-0.5%
3. antihistamines: 0.1-2%
4. local anesthetics: 0.05-2%

5. bacteriocides and disinfectants: 0.01-10%
6. vasoconstrictors: 0.01-1%
7. hemostatics: 0.05-1%
8. chemotherapeutics: 0.05-1%
9. antibiotics: 0.001-10%
10. cosmetics
11. tooth desensitizing agents: 0.1-10%
12. antifungals: 0.1-10%
13. vasodilators: 0.1-10%
14. antihypertensives: 0.1-10%
15. antiemetics: 0.1-10%
16. antimigraine: 0.1-10%
17. antiarrhythmics: 0.1-10%
18. antiasthmatics: 0.1-10%
19. antidepressants: 0.1-10%
20. vaccines: 0.1-1%
21. peptides: 0.1-1%
22. hormones: 0.1-1%
23. anti-proton pumps or H receptor blockers: 0.1-10%
24. smoking cessation aids: 1-5%

Examples of anti-inflammatory, analgesic agents include acetaminophen, methyl salicylate, monoglycol salicylate, aspirin, mefenamic acid, flufenamic acid, indomethacin, diclofenac, alclofenac, diclofenac sodium, ibuprofen, flurbiprofen, fentizac, bufexamac, piroxicam, phenylbutazone, oxyphenbutazone, clofezone, pentazocine, mepirizole, and tiaramide hydrochloride.

Examples of steroidal anti-inflammatory agents include hydrocortisone, predonisolone, dexamethasone, triamcinolone acetonide, fluocinolone acetonide, hydrocortisone acetate, predonisolone acetate, methylpredonisolone, dexamethasone acetate, betamethasone, betamethasone valerate, flumetasone, flourometholone, beclomethasone dipropionate, and budesonide.

Examples of antihistamines include diphenhydramine hydrochloride, diphenhydramine salicylate, diphenhydramine, chlorpheniramine hydrochloride, chlorpheniramine maleate, isothipendyl hydrochloride, tripelennamine hydrochloride, promethazine hydrochloride, and methdilazine hydrochloride.

Examples of local anesthetics include dibucaine hydrochloride, dibucaine, lidocaine hydrochloride, lidocaine, benzocaine, p-buthylaminobenzoic acid 2-(diethylamino) ethyl ester hydrochloride, procaine hydrochloride, tetracaine hydrochloride, chloroprocaine hydrochloride, oxyprocaine hydrochloride, mepivacaine, cocaine hydrochloride, and piperocaine hydrochloride.

Examples of bacteriocides and disinfectants include thimerosol, phenol, thymol, benzalkonium chloride, benzethonium chloride, chlorhexidine, providone iodide, cetylpyridinium chloride, eugenol, and trimethylammonium bromide.

Examples of vasoconstrictors include naphazoline nitrate, tetrahydrozoline hydrochloride, oxymetazoline hydrochloride, phenylephrine hydrochloride, and tramazoline hydrochloride.

Examples of hemostatics include thrombin, phytonadione, protamine sulfate, aminocaproic acid, tranexamic acid, carbazochrome, carbaxochrome sodium sulfonate, rutin, and hesperidin.

Examples of chemotherapeutic drugs include vinblastine, cis-platin, 5-fluorouracil (5FU), methotrexate (MTX), 6 mercaptopurine (6MP), 1-β-D-arabinofuranosylcytosine (ara-C), mechlorethamine, chlorambucil, melphalan oxazaphosphorines, carboplatin, JM40, spiroplatin, tetraplatin, JM216, and taxol.

Examples of antibiotics include penicillin, meticillin, oxacillin, cefalotin, cefaloridin, erythromycin, lincomycin, tetracycline, chlortetracycline, oxytetracycline, metacycline, chloramphenicol, kanamycin, streptomycin, gentamicin, bacitracin, and cycloserine.

Examples of antifungal drugs include amphotericin, clotrimazole, econazole nitrate, fluconazole, grisofulvin, itraconazole, ketoconazole, miconazole, nystatin, terbinafine hydrochloride, undecenoic acid, and zinc undeconoate.

Examples of vasodilator drugs include buflomedil hydrochloride, bucheneine hydrochloride, naftidrofury oxalate, oxpentifylline, glyceryl trinitrate, isosorbide dinitrate, isosorbide mononitrate and pentaerythritol tetranitrate.

Examples of antihypertensive drugs include amlodipine, benazepril hydrochloride, captopril, clonidine hydrochloride, diazoxide, diltiazem, hydrochloride, enalapril maleate, enalaprilat, felodipine, isradipine, nicardipine hydrochloride, nifedipine, atenolol, metoprolol tartarate, oxpenolol hydrochloride, propranolol hydrochloride and verapamil hydrochloride.

Examples of antiarrhythmic drugs include quinidine, quinidine salts, procainamide hydrochloride, lidocaine, and mexiletine hydrochloride.

Examples of antiemetic drugs include metoclopramide hydrochloride, nabilone, and ondansetron hydrochloride.

Examples of proton pump inhibitors or H receptor blockers include omeprazole, ranitidine and cimetidine.

Examples of antimigraine drugs include dihydroergotamine mesylate, ergotamine tartarate, sumatriptan succinate and other triptan drugs.

Examples of peptide or protein drugs include insulin, buserelin acetate, goserlin acetate, leuprorelin acetate, calcitonin, cyclosporin, gonadorelin, somastatin, vasopressin, oxytocin, interferon, and human growth hormone.

Examples of antidepressant drugs include fluoxetine hydrochloride, imipramine, maprotiline hydrochloride, and phenelzine sulfate.

Examples of antiasthmatics include salbutamol and terbutaline sulfate.

Examples of smoking cessation aids include nicotine, nicotine salts, nicotine polymer complexes, and cotinine.

Examples of cosmetics include breath fresheners and tooth whiteners.

When release of the agent is localized to the teeth, preferred agents include tooth-whitening agents, such as carbamide peroxide, and tooth-desensitizing agents, such as potassium nitrate and strontium chloride.

The conditions amenable to treatment with the patch described herein include, but are not limited to oral infections, lesions, low or high blood pressure,

Helicobacter infections, pain, cough, migraine, vomiting, nausea, inflammation, sleep apnea, snoring, gerd and reflux disease. Preferred conditions include yeast infections, periodontal diseases, snoring, oral ulcers or other lesions.

The invention will now be illustrated in greater detail with reference to the following examples, but it should be understood that these are not intended to limit the present invention.

Examples

Example 1

Prolonged Sustained Release of Highly Soluble Drugs

Materials and Methods

Hydrolyzed gelatin was purchased from Croda.
Tannic acid USP was purchased from Merck.
Nicotine was purchased from The Nicobrand Company.
Pilocarpine was purchased from Laob.

Preparation of Formulations

Hydrolyzed gelatin and the drug (nicotine or pilocarpine) were dissolved in a mixture of ethanol and water (or water alone). A solution of tannic acid in water and ethanol (or water alone) was added. The precipitate that formed was air-dried to constant weight and ground to a powder.

In Vitro Release Experiments

The powder (0.5 gm) was inserted into dialysis bags which were stirred in 100 ml phosphate buffer (0.01M, pH 7.4) at room temperature. Samples of 0.5 ml were taken for analysis.

Results

Formulations of nicotine and pilocarpine, both highly soluble drugs, were prepared. These formulations, used to illustrate the controlled release of highly soluble drugs, are given in Tables 1-2.

Table 1: Liquid Formulation 245-49 (nicotine)	
Ingredient	Weight %
Hydrolyzed gelatin	10
1N HCl	6
Nicotine	1
Ethanol	40
Water	33
Tannic acid	10

Table 2: Liquid Formulation 245-43C (pilocarpine)	
Ingredient	Weight %
Pilocarpine	0.3
Hydrolyzed gelatin	9
Tannic acid	9
Water	81.7

The *in vitro* release of the active ingredients from the powders obtained from these formulations was tested. The results are summarized in Tables 3-4.

Table 3: *In Vitro* Release of Nicotine from Formulation 245-49

Time (hr)	% Cum Rel	% Cum Rel
0.25	1.99	3.50
0.5	3.19	5.45
1	5.18	7.39
2	8.76	10.50
3	12.35	16.34
4	17.93	23.35
5	21.91	26.85
6	25.10	30.74
7	27.09	35.80

Table 4: *In Vitro* Release of Pilocarpine from Formulation 245-43C

Time (hr)	% Cum Rel
0.25	2.77
0.5	5.03
1	7.28
2	14.22
3	19.77
4	25.32
5	31.56
6	37.46
7	42.66
8	47.86

The results show that one can control the release of highly soluble drugs with these formulations. The release can take place over many hours with less than half the drug having been released in eight hours.

Example 2

Control Over the Rate of Drug Release in Prolonged Controlled Release of a Highly Soluble Drug: I

Materials and Methods

Hydrolyzed gelatin was purchased from Croda.

Tannic acid USP was purchased from Merck.

Sodium salicylate was purchased from Merck.

Preparation of Formulation

The powder of gelatin-tannic acid was formulated with the highly soluble drug sodium salicylate and prepared using two different ratios of ethanol and water. In formulation 245-66A the weight proportion of the solvent was 3:1 (ethanol : water) and in formulation 245-68A it was 1:1.

Results

The formulations used are described in Tables 5-6.

Table 5: Liquid Formulation 245-66A	
Ingredient	Weight %
Hydrolyzed gelatin	10
Sodium Salicylate	1
Water	19
Ethanol	60
Tannic acid	10

Table 6: Liquid Formulation 245-68A	
Ingredient	Weight %
Hydrolyzed gelatin	10
Sodium Salicylate	1
Water	39.5
Tannic acid	10
Ethanol	39.5

In vitro release studies were carried out on the powders obtained from these formulations as in Example 1.

The results of the *in vitro* release studies are summarized in Tables 7 and 8.

Table 7: *In Vitro* Release of Sodium Salicylate from Formulation 245-66A		
Time (hr)	% Cumulative Release	% Cumulative Release
0.25	15	24
0.5	21	34
1	29	45
2	40	57
3	45	66
4	52	70
5	59	78
6	68	83
7	74	86

Table 8: *In Vitro* Release of Sodium Salicylate from Formulation 245-68A		
Time (hr)	% Cumulative Release	% Cumulative Release
0.25	9	14
0.5	15	20
1	22	29
2	32	39
3	39	47
4	44	52
5	49	56
6	52	60
7	55	64

One can see that a high proportion of water in the solvent mixture decreases the release rate of the active ingredient while a higher ethanol content

increases the release rate. In both cases one has prolonged release of the highly soluble substance, sodium salicylate, from the matrix.

Example 3

Control Over the Rate of Drug Release in Prolonged Controlled Release of a Highly Soluble Drug: II

Materials

Hydrolyzed gelatin was purchased from Croda.

Tannic acid USP was purchased from Merck.

Nicotine was purchased from The Nicobrand Company.

Preparation of Formulation

The powder of gelatin-tannic acid was formulated with the highly soluble drug nicotine and prepared using two different ratios of ethanol and water. In formulation 245-70 the weight proportion of the solvent was 3:1 (ethanol:water) and in formulation 245-49 it was 1:1.

Results

The formulations are given in Tables 9 and 10.

Table 9: Liquid Formulation 245-70	
Ingredient	Weight %
Hydrolyzed gelatin	10
1N HCl	5
Nicotine	1
Water	17
Ethanol	57
Tannic acid	10

Table 10: Liquid Formulation 245-49	
Ingredient	Weight %
Hydrolyzed gelatin	10
1 N HCl	6
Nicotine	1
Water	34
Ethanol	39
Tannic acid	10

In vitro release studies were carried out on the powders obtained from these formulations as in Example 1.

The release pattern of nicotine from formulations 245-70 and 241-49 is illustrated in Tables 11 and 12.

Table 11: Release of Nicotine from formulation 245-70		
Time (hr)	% Cumulative Release	% Cumulative Release
0.25	15	12
0.5	20	17
1	28	25
2	38	35
3	43	42
4	45	46
5	46	52
6	49	55
7	49	56

Table 12: Release of Nicotine from formulation 245-49		
Time (hr)	% Cumulative Release	% Cumulative Release
0.25	4.5	4
0.5	6	5
1	7	7
2	11	10
3	13	11
4	15	14
5	17	16
6	19	18
7	20	19

As it was shown for sodium salicylate, the effect of the solvent mixture was achieved with nicotine also. Increased amounts of water in the solvent mixture during the preparation of the formulation results in slower release.

Example 4

Prolonged Sustained Release of Nicotine from a Pharmaceutical Oral Patch

Materials

Hydrolyzed gelatin was purchased from Croda.

Tannic acid USP was purchased from Merck.

Eudragit L-100, Eudragit 30D-55 and triethyl citrate NF were purchased from Rhöm Pharma.

Nicotine was purchased from The Nicobrand Company.

Preparation of Formulations

The patch was formed by mixing the powder formed from Formulation 245-70 (Table 9) with an ethanolic solution of Eudragit L-100 and a plasticizer.

The mixture was transferred to plastic molds and dried to form an adhesive pharmaceutical oral patch.

In Vitro Release

The dry patches (300 mg) were stirred in 100 ml buffer (phosphate, 0.01 M, pH 7.4) at room temperature. Samples of the solution (0.5 ml) were analyzed.

Results

In vitro release experiments were carried out. The results are summarized in Table 13.

Table 13: *In Vitro* Release of Nicotine from a Pharmaceutical Oral Patch		
Time (hr)	% Cumulative Release	% Cumulative Release
0.25	2	3.5
0.5	3.2	5.5
1	5.2	7.4
2	8.8	10.5
3	12.4	16.3
4	17.9	23.4
5	21.9	26.9
6	25.1	30.7
7	27.1	35.8

Example 5

Prolonged Sustained Release of Pilocarpine from a Pharmaceutical Oral Patch

Materials

Hydrolyzed gelatin was purchased from Croda.

Tannic acid USP was purchased from Merck.

Eudragit L-100, Eudragit 30D-55 and triethyl citrate NF were purchased from Rhöm Pharma.

Pilocarpine was purchased from Laob.

Preparation of Formulations

The patch was formed by mixing the powder formed from Formulation 245-43C (Table 2) with a water suspension of Eudragit L 30D-55.

The mixture was transferred to plastic molds and dried to form a pharmaceutical oral patch.

In Vitro Release

The dry patches (300 mg) were stirred in 100 ml buffer (phosphate, 0.01M, pH 7.4) at room temperature. Samples (0.5 ml) of the solution were analyzed.

Results

In vitro release experiments were carried out. The results are summarized in Table 14.

Table 14: *In Vitro* Release of Pilocarpine from a Pharmaceutical Oral Patch

Time (hr)	% Cumulative Release	% Cumulative Release
0.25	7.9	4.3
0.5	11.6	6.2
1	16.1	8.5
2	21	12
3	27	15.1
4	31.1	17.8
5	32.6	21.6

The results show that one can control the release of soluble drugs from a pharmaceutical oral patch for several hours.

Example 6

In Vitro Release of Nicotine from an Adhesive Pharmaceutical Oral Patch

Materials

Hydrolyzed gelatin was purchased from Croda.

Tannic acid USP was purchased from Merck.

Eudragit L-100 and Triethyl Citrate NF were purchased from Rhom Pharma.

Nicotine was purchased from The Nicobrand Company.

Preparation of Formulations

The patch was formed by mixing the powder formed from liquid Formulation 158-72 (Table 15), with an ethanolic solution of Eudragit L-100 and a plasticizer.

The mixture was transferred to plastic molds and dried to form an adhesive pharmaceutical oral patch.

Table 15: Liquid Formulation 158-72

Ingredient	Weight %
Hydrolyzed gelatin	28
37% HCl	0.5
Nicotine	1
Water	47.5
Ethanol	3
Tannic acid	20

In Vivo Release Experiment

The pharmaceutical oral patch (190 mg), containing 2 mg nicotine, was attached to the buccal side of an upper molar tooth by means of self adhesion.

Saliva samples were expectorated at given time intervals and tested for nicotine content.

Results

One volunteer wore the pharmaceutical oral patch for a period of four hours. The patch conformed to the contour of the tooth and was comfortable to wear. Saliva samples were collected and analyzed by chromatography. The results are listed in Table 16.

Table 16: In Vivo Release of Nicotine from a Pharmaceutical Oral Patch

Time (min)	Concentration (ppm)
0	0.3
15	13.4
30	25.1
60	23.8
90	51.6
120	20.1
180	26.3
240	18.1

The results indicate that clinically significant concentrations of nicotine as an example of soluble drug, can be maintained in the oral cavity for several hours. The pharmaceutical oral patch self-adhered to the tooth for the entire period of the experiment.

Example 7

In Vivo Release of Nicotine from a Second Adhesive Pharmaceutical Oral Patch

Materials

Hydrolyzed gelatin was purchased from Croda.

Tannic acid USP was purchased from Merck.

Eudragit 30D-55 and Triethyl Citrate NF were purchased from Rhöm Pharma.

Nicotine was purchased from The Nicobrand Company.

Preparation of Formulations

The patch was formed by mixing the powder formed from liquid Formulation 41B001SL (Table 17) with an aqueous suspension of Eudragit L 30D-55 and a plasticizer.

The mixture was transferred to plastic molds and dried to form an adhesive pharmaceutical oral patch.

Table 17: Liquid Formulation 41B001SL

Ingredient	Weight %
Hydrolyzed gelatin	27.5
37% HCl	1
Nicotine	1.6
Water	46.5
Ethanol	3.2
Tannic acid	20.1

In Vivo Release Experiment

The pharmaceutical oral patch (115 mg), containing 2 mg nicotine, was attached to the buccal side of an upper molar tooth by means of self adhesion.

Saliva samples were expectorated at given time intervals and tested for nicotine content.

Results

One volunteer wore the pharmaceutical oral patch for a period of four hours. The patch conformed to the contour of the tooth and was comfortable to wear. Saliva samples were collected and analyzed by chromatography. The results are listed in Table 18.

Table 18: *In Vivo* Release of Nicotine from a Pharmaceutical Oral Patch

Time (min)	Concentration (ppm)
0	0.3
30	2.7
60	5.6
120	11.3
180	28.6
240	0.7

The results indicate that clinically significant concentrations of nicotine can be maintained in the oral cavity for several hours. The pharmaceutical oral patch self adhered to the tooth for the entire period of the experiment.

Example 8

Release of Liposome Encapsulated Nicotine from Pharmaceutical Oral Patches

Nicotine was entrapped in liposomes of both the multilamellar vesicle (MLV) and small unilamellar vesicle (SUV) type. The formulations used for the formation of the liposomes are given in Table 19.

Table 19: Ingredients of MLV and SUV Liposomes:

Type	Materials	weight(g)	mole%
Nicotine Liposomes MLV	Egg Phosphatidylcholine (PC) 99% Synthetic	1	60.9
	Phosphatidylethanolamine (PE) 99%	0.1	6.6
	Cholesterol 95%	0.275	32.5
Nicotine Liposomes SUV	Soybean Phosphatidylcholine (PC) Synthetic	1.2	62.8
	Phosphatidylethanolamine (PE) 99%	0.12	6.8
	Cholesterol 95%	0.3	30.4

The phospholipids and lipids were dissolved in 25 ml chloroform:methanol (2:1) in a round bottom flask of 100-1000 ml. The lipid solution was dried for 2 hours to form a lipid film onto the sides of the flask, using a rotary evaporator apparatus. The lipids were hydrated by addition of 10-20 ml H_2O or PBS (phosphate buffered saline) solution (0.01 M, pH 7.4), followed by vortexing and shaking in a 37°C water bath, for 2-4 hours to form MLV liposomes. The liposomes were characterized by standard chemical and electron microscope techniques.

MLV Nicotine Liposomes:

Nicotine (0.2 ml), a volatile and water soluble drug, was dissolved in an aqueous medium and added to the lipid film at the hydration step.

SUV Nicotine Liposomes:

Nicotine (0.2 ml), in an aqueous medium was added to placebo liposomes (MLV) followed by 1 hour sonication to form nicotine liposomes of type SUV.

The percent entrapment of the nicotine was determined for each type of liposome and is shown in Table 20.

Table 20: Efficiency of Nicotine Encapsulation in Liposomes:

Type of liposomes	% of encapsulation
SUV	36
MLV	15

One can see that nicotine encapsulation in the liposomes was as expected for a water soluble drug. More drug was encapsulated in the SUV than in the MLV due to the higher percent internal aqueous volume in this form of liposome.

The liposomes were stored at 4°C (closed tightly).

Pharmaceutical oral patches were made using nicotine trapped in MLV liposomes with and without an outer polymer matrix. The other ingredients of the patches are given in Table 21.

Table 21: Non Active Ingredients of Patches:

Materials	Batch# 285-23A wgt (g)	Batch# 285-23B wgt (g)	Batch# 285-28 wgt (g)	Batch# 49A004 wgt (g)	Batch# 158-64 wgt (g)
H_2O	3.3	3.3	3.1	33	33
BycoE	2.6	2.6	3.1	26	26
H_2O	1.1	1.1	1.3	11	11
Ethanol	0.3	0.3	-	3	3
Tannic Acid	1.9	1.9	1.7	19	19
Matrix (Eudr.L-30D+Glycerin)	+	-	-	-	-
Matrix (Eudr.L-100+Ethanol)	-	+	-	+	+

Patches of Batches# 285-23A, 285-23B:

2g of MLV liposomes containing entrapped nicotine were suspended in water. BycoE™ was added and finally a solution of tannic acid in ethanol-water was added. The precipitate was dried at 50°C, ground to a powder and mixed with a polymer matrix based on Eudragit™ (approx. 1:1). Polypropylene molds were filled with the mixture (190mg/well) and dried at 35°C. These patches contain ~2 mg nicotine each and are formed with an outer polymer matrix.

Patches of Batch# 285-28:

Solution of tannic acid in water was added dropwise into solution of Byco E™. 0.45g of the tannic acid-Byco preparation were mixed with 0.63g of MLV liposomes containing entrapped nicotine. Polypropylene molds were filled with the mixture (280mg/well) and dried at 35°C in the oven. These patches contain ~2 mg nicotine each and are formed without an outer polymer matrix.

Patches without liposomes # 49A004 and 158-64:

Nicotine neutralized with HCl was dissolved in water. Byco E™ was added and finally a solution of tannic acid in ethanol-water was added. The precipitate was dried at 50°C, ground to a powder and mixed with a polymer matrix based on Eudragit™ (approx. 1:1). Polypropylene molds were filled with the mixture (190mg/well) and dried at 35°C. These patches contain ~2 mg nicotine each and are formed with an outer polymer matrix.

Release Assays:

***In vitro*:** Patches containing liposomes were introduced into dialysis tubes with a molecular weight cutoff of 50,000 and stirred in bulk solutions of 50-100 ml phosphate buffered saline (PBS) (0.01M, pH 7.4). 0.2ml samples were collected at times 0-7h. The nicotine was determined by a validated HPLC method.

In vivo: The pharmaceutical oral patch was attached to an upper back tooth. Saliva samples were collected at times 0-180 min. The nicotine was determined by a validated HPLC method.

Results *in Vitro*:

The average results of release of nicotine from the *in vitro* pharmaceutical oral patches are summarized in Figure 1.

The release of drug from liposomal patches #285-28 (V) was slower than from the non liposomal nicotine patches #49A004 (VI-VIII). The release of nicotine from both of these types of patches was characterized by a single rate constant. In contrast, the release profile of nicotine from liposomal patches #285-23A (I and II) and #285-23B (III and IV), was characterized by a two phase release of the drug and was also slower than the non-liposomal formulation.

Results *in Vivo*:

The release experiment of nicotine *in vivo* was performed, using patch #285-28 containing centrifuged nicotine liposomes type MLV and compared to non-liposomal nicotine patch #158-64. The results are shown in Figure 2.

One sees that salivary concentrations of nicotine were higher for the formulation without liposomes. The profiles of release were similar.

Example 9

Release of Liposome Encapsulated Flurbiprofen from Pharmaceutical Oral Patches

Flurbiprofen was entrapped in multilamellar vesicle type liposomes as follows:

Soybean phosphatidylcholine (14 gm) was dissolved in 100 ml ethanol in a 1000 ml round bottom flask along with 2.3 gm flurbiprofen. The lipid solution

was dried for 1.5 hours to form a lipid film with flurbiprofen dispersed therein, onto the sides of the flask, using a rotary evaporator apparatus. The lipids were hydrated by addition of 140 ml H_2O, followed by rotation for 2 hours and slow stirring for 1 hour to form MLV liposomes. The liposomes were characterized by standard chemical and electron microscope techniques. The non-encapsulated flurbiprofen was removed by dialysis. The liposomes were obtained by centrifugation at 10°C for 1 hour at 17500 rpm.

Patches of Batch# 285- 62:

Tannic acid (1.7 gm) in 1.3 gm water was added dropwise to a solution of 3.1 gm hydrolyzed gelatin (BycoE™) in water. The tannic acid - hydrolyzed gelatin preparation was mixed with 9.6 gm of MLV liposomes containing entrapped flurbiprofen. Polypropylene molds were filled with the mixture (200 mg/well) and the patches were dried in an oven at 30°C.

Release Assays:

In vitro: Patches containing liposomes were stirred in bulk solutions of 100 ml PBS (0.01 M, pH 7.4). 0.2ml samples were collected at times 0-7h. The flurbiprofen was determined by a validated HPLC method.

Results *in Vitro*:

The average results of the *in vitro* release of flurbiprofen from the pharmaceutical oral patches are summarized in Figure 3 and Table 22. One can see clear sustained release of the flurbiprofen from the patches.

Table 22: Cumulative Release of Flurbiprofen

Time	% cumulative release
0	0
15	7.53
30	10.94
60	15.37

120	21.12
180	27.19
240	30.81
300	33.66
360	37.44

What Is Claimed Is:

1. A liquid composition comprising hydrolyzed gelatin and tannic acid or tannin.

2. A liquid composition comprising hydroxypropylmethylcellulose and tannic acid or tannin.

3. A liquid composition consisting essentially of hydroxyethylcellulose and tannic acid or tannin.

4. A liquid composition comprising a protein and tannic acid or tannin, wherein said liquid composition dries to form a solid composition capable of controlled release of a pharmaceutical compound therefrom or forms a precipitate of said protein and tannic acid or tannin that dries to form a solid composition capable of controlled release of a pharmaceutical compound therefrom.

5. The liquid composition of claim 4 wherein said protein is selected from the group consisting of gelatin, hydrolyzed gelatin, collagen and albumin.

6. A liquid composition comprising a cellulosic polymer selected from the group consisting of hydroxyethylcellulose and hydroxypropylmethylcellulose, and tannic acid or tannin, wherein said liquid composition dries to form a solid composition capable of controlled release of a pharmaceutical compound therefrom.

7. A liquid composition comprising a protein and tannic acid or tannin, wherein said liquid composition dries to form an adhesive solid composition capable of controlled release of a pharmaceutical compound

therefrom or forms a precipitate of said protein and tannic acid or tannin that dries to form a solid composition capable of controlled release of a pharmaceutical compound therefrom.

8. The liquid composition of claim 7 wherein said protein is selected from the group consisting of gelatin, hydrolyzed gelatin, collagen and albumin.

9. A liquid composition comprising a cellulosic polymer selected from the group consisting of hydroxyethylcellulose and hydroxypropylmethylcellulose, and tannic acid or tannin, wherein said liquid composition dries to form an adhesive solid composition capable of controlled release of a pharmaceutical compound therefrom.

10. A liquid composition comprising a protein selected from the group consisting of hydrolyzed gelatin, albumin, and collagen, and tannic acid or tannin and a pharmaceutical compound.

11. A liquid composition comprising hydroxypropylmethylcellulose and tannic acid or tannin and a pharmaceutical compound.

12. A liquid composition comprising a mixture of a protein and tannic acid or tannin and a pharmaceutical compound.

13. The liquid composition of claim 12 wherein said protein is selected from the group consisting of gelatin, hydrolyzed gelatin, albumin, and collagen.

14. A liquid composition comprising a mixture of hydroxyethylcellulose and tannic acid or tannin and a pharmaceutical compound.

15. A liquid composition comprising a protein and tannic acid or tannin, and a pharmaceutical, wherein said liquid composition dries to form a solid composition capable of controlled release of said pharmaceutical therefrom or forms a precipitate of said protein and tannic acid or tannin that dries to form a solid composition capable of controlled release of a pharmaceutical compound therefrom.

16. The liquid composition of claim 15 wherein said protein is selected from the group consisting of gelatin, hydrolyzed gelatin, collagen and albumin.

17. A liquid composition comprising a cellulosic polymer selected from the group consisting of hydroxyethylcellulose and hydroxypropylmethylcellulose, and tannic acid or tannin, and a pharmaceutical, wherein said liquid composition dries to form a solid composition capable of controlled release of a pharmaceutical compound therefrom.

18. A liquid composition comprising a protein and tannic acid or tannin, and a pharmaceutical, wherein said liquid composition dries to form an adhesive solid composition capable of controlled release of said pharmaceutical therefrom or forms a precipitate of said protein and tannic acid or tannin that dries to form a solid composition capable of controlled release of a pharmaceutical compound therefrom.

19. The liquid composition of claim 18 wherein said protein is selected from the group consisting of gelatin, hydrolyzed gelatin, collagen and albumin, and tannic acid or tannin.

20. A liquid composition comprising a cellulosic polymer selected from the group consisting of hydroxyethylcellulose and hydroxypropylmethylcellulose, and tannic acid or tannin, and a pharmaceutical, wherein said liquid composition

dries to form an adhesive solid composition capable of controlled release of a pharmaceutical therefrom.

21. A liquid composition of claims 15, 17, 18 or 20 wherein the pharmaceutical agent is entrapped in liposomes or microcapsules, microspheres, nanocapsules or nanospheres.

22. A liquid composition according to claim 21 where said liposome comprises phospholipids and/or sphingolipids such as soybean lecithin, egg lecithin, soybean phosphatidylcholine, egg phosphatidylcholine, synthetic phosphatidylcholine, phosphatidylserine, phosphatidylinositol, phosphatidylglycerol, phosphatidylethanolamine, and sphingomyelin alone or in mixtures.

23. A liquid composition according to claim 21 where said microcapsule, microsphere, nanocapsule or nanosphere comprises polymers such as polyalkyl methacrylate such as polymethylmethacrylate, polyalkylcyanoacrylates such as polymethylcyanomethacrylate, polyesters such as polylactic acid and polylactic/glycolic acid copolymers, cellulose derivatives such as ethylcellulose and cellulose acetate and proteins such as albumin, gelatin, and hydrolyzed gelatin, and polysaccharides such as sodium alginate, pectin, chitosan, guar gum, and xanthan gum.

24. A solid composition comprising a cellulosic polymer selected from the group consisting of hydroxyethylcellulose and hydroxypropylmethylcellulose and tannic acid or tannin, and a pharmaceutical, wherein said solid composition is capable of controlled release of said pharmaceutical therefrom.

25. A solid composition comprising a mixture of a protein, and tannic acid or tannin, and a pharmaceutical, wherein said solid composition is capable of controlled release of said pharmaceutical therefrom.

26. The solid composition of claim 22 wherein said protein is selected from the group consisting of gelatin, hydrolyzed gelatin, albumin, and collagen.

27. A solid adhesive composition comprising a protein, and tannic acid or tannin, and a pharmaceutical, wherein said solid adhesive composition is capable of controlled release of said pharmaceutical therefrom.

28. The solid adhesive composition of claim 24 wherein said protein is selected from the group consisting of gelatin, hydrolyzed gelatin, albumin, and collagen.

29. A solid adhesive composition comprising a pharmaceutical and a cellulosic polymer selected from the group consisting of hydroxyethylcellulose and hydroxypropylmethylcellulose and tannic acid or tannin, wherein said solid adhesive composition is capable of controlled release of said pharmaceutical therefrom.

30. A method for producing a solid composition capable of the controlled release of a pharmaceutical, said method comprising:

(1) providing a protein, tannic acid or tannin, and a pharmaceutical, in a liquid solution of a solvent selected from the group consisting of water, alcohol and water:alcohol,

(2) allowing a precipitate to form between the protein and tannic acid or tannin, thus entrapping the pharmaceutical in the precipitate,

(3) allowing said precipitate to dry, thereby forming said solid composition.

31. The method of claim 27, wherein release of said pharmaceutical from said solid composition is controlled by the alcohol:water ratio of said solution.

32. The method of claim 27, wherein release of said pharmaceutical is controlled by the further steps of:

(1) adding a second polymer selected from the group consisting of Eudragit™ polymers, hydroxypropylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose, pectin, calcium pectinate, alginic acid, calcium alginate, cellulose acetate phthalate, carbopol, guar gum, gum tragacanth, gum acacia, and chitosan, in solution or suspension and a plasticizer to said dried precipitate,

(2) allowing the components in step (1) to dry.

33. The method of claim 29, wherein said Eudragit™ polymer is selected from the group consisting of Eudragit™ L-100, Eudragit™ L 30D-55, Eudragit™ S-100, Eudragit™ NE-100, Eudragit™ NE-30, Eudragit™ RL, and Eudragit™ RS.

34. The method of claim 29, wherein controlled release is further adjusted by the alcohol:water ratio in said solution.

35. The method of either of claims 28 or 31, wherein said alcohol is ethanol.

36. The method of claim 29 wherein the release of said pharmaceutical is further controlled by the addition of pH adjusting agents, release adjusting agents, or solubility adjusting agents, to the solution or suspension of the second polymer.

37. The method of claim 29 wherein said pharmaceutical or a different pharmaceutical is included in the solution or suspension of said second polymer.

38. The method of any of claims 27-32, wherein said protein is selected from the group consisting of gelatin, hydrolyzed gelatin, albumin, and collagen.

39. A method of using the compositions of any of claims 22-26, wherein said composition is used to release a pharmaceutical into the oral cavity.

40. The method of claim 36, wherein the form of said composition is as a tooth patch as described herein.

41. The method of claim 37, wherein said pharmaceutical is selected from the group consisting of nicotine, nicotine salts, nicotine polymer complexes, lidocaine, piroxicam, flurbiprofen, dihydroergotamine mesylate, ergotamine tartarate, sumatriptan succinate, isosorbide dinitrate, isosorbide mononitrate, nifedipine, ondansetron hydrochloride, and peptide drugs.

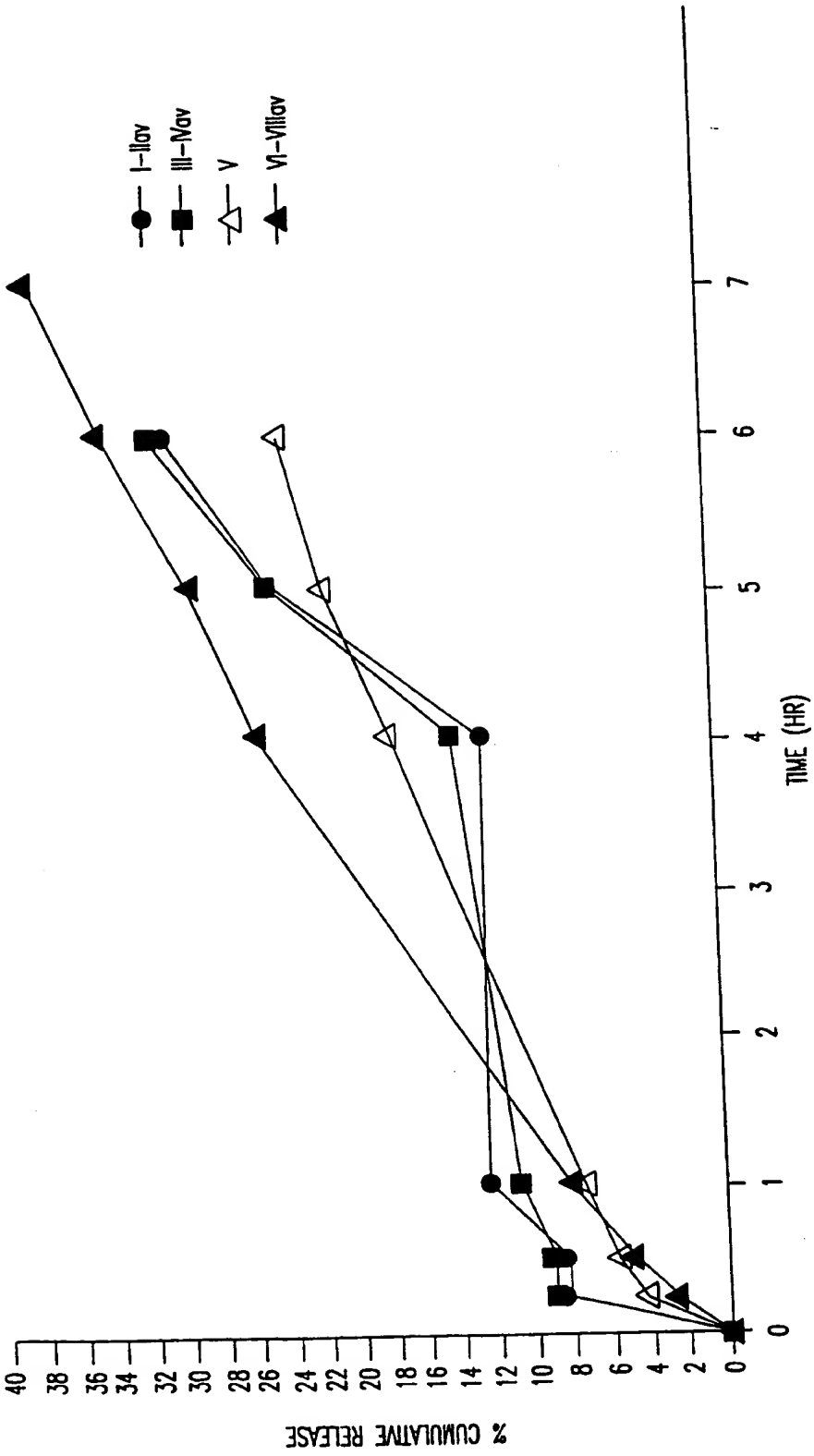
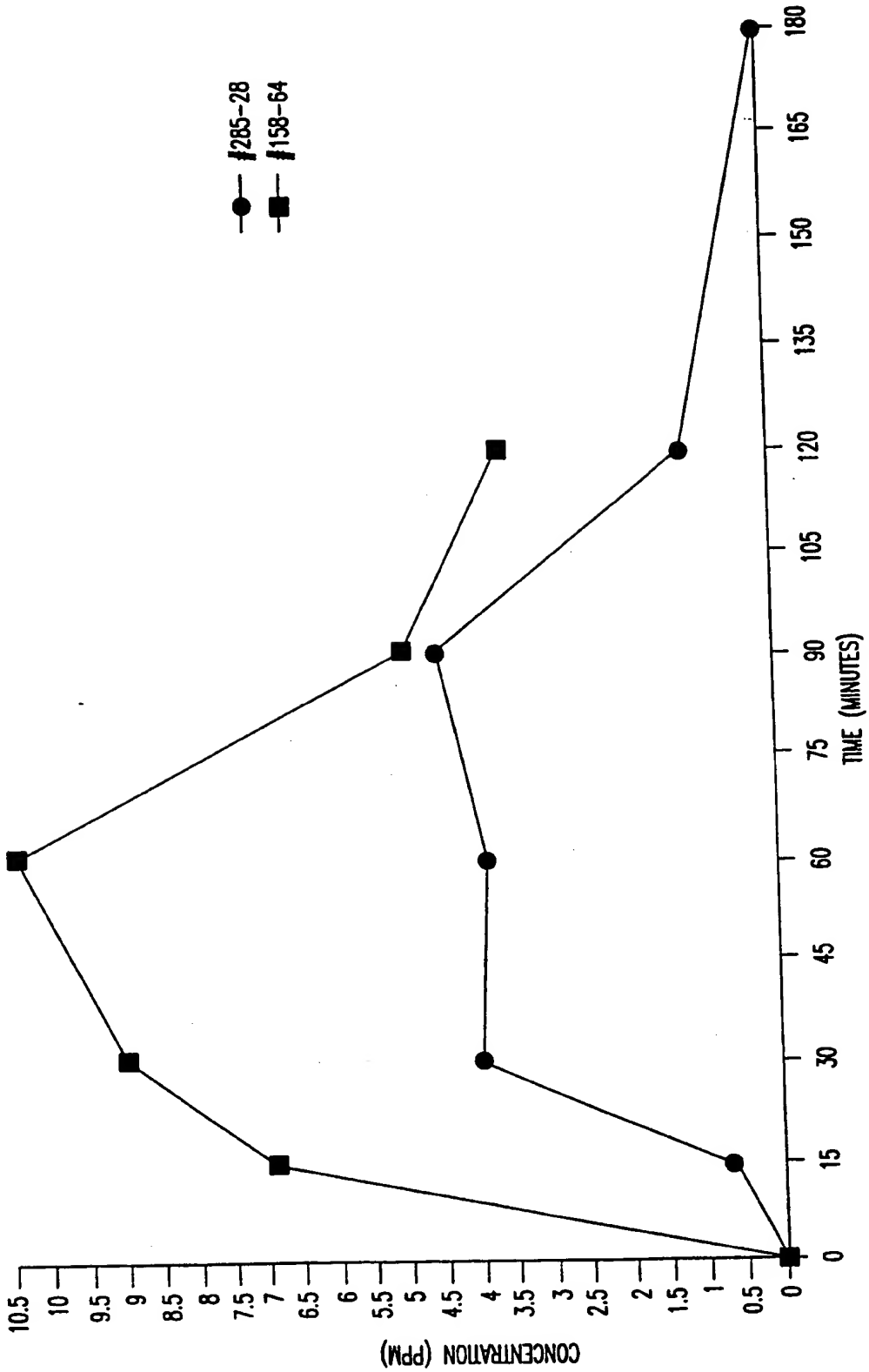

I-IIav
III-IVav
V
VI-VIIIav
% CUMULATIVE RELEASE
0
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30
32
34
36
38
40
TIME (HR)
0
1
2
3
4
5
6
7

FIG.1


#285-28
#158-64
CONCENTRATION (PPM)
TIME (MINUTES)
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0.5
1
1.5
2
2.5
3
3.5
4
4.5
5
5.5
6
6.5
7
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8
8.5
9
9.5
10
10.5
0
15
30
45
60
75
90
105
120
135
150
165
180

FIG.2

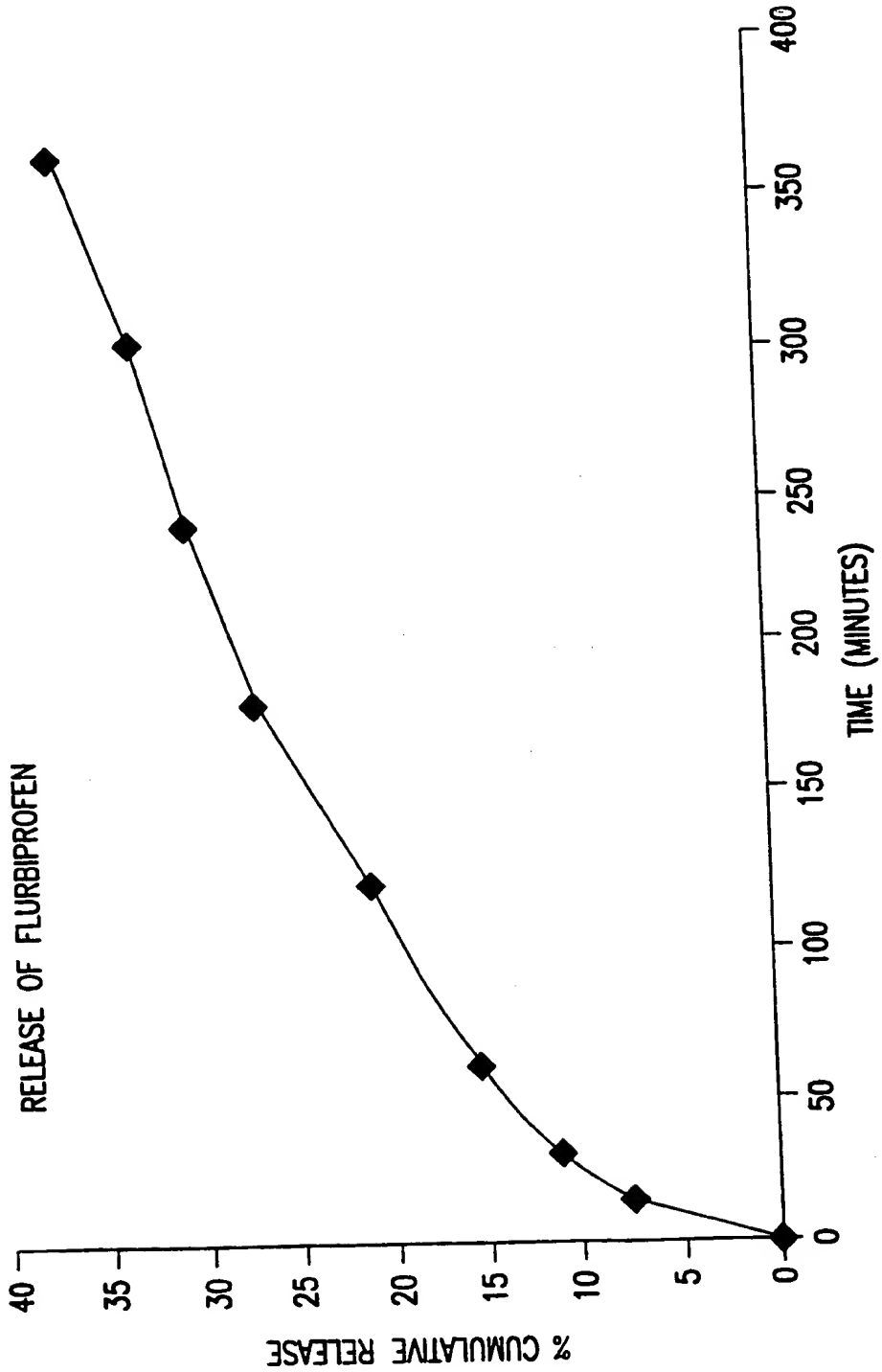
RELEASE OF FLURBIPROFEN
% CUMULATIVE RELEASE
0
5
10
15
20
25
30
35
40
TIME (MINUTES)
0
50
100
150
200
250
300
350
400

FIG.3

INTERNATIONAL SEARCH REPORT

Interi nal Application No
PCT/US 98/15096

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/20 A61K9/70

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PATENT ABSTRACTS OF JAPAN vol. 097, no. 004, 30 April 1997 & JP 08 319232 A (TAKEDA CHEM IND LTD), 3 December 1996 see abstract	4,5,7,8, 10,12, 13,15, 16,18, 19,25-28
X	& DATABASE WPI Section Ch, Week 9707 Derwent Publications Ltd., London, GB; Class B03, AN 97-073079 & JP 08 319232 A (TAKEDA CHEM IND LTD) see abstract	4,5,7,8, 10,12, 13,15, 16,18, 19,25-28
X	GB 2 036 750 A (PAYNE M) 2 July 1980 see page 1 - page 2; example 1	4,5,7,8

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 December 1998	11/12/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Boulois, D

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INTERNATIONAL SEARCH REPORT

Interr nal Application No
PCT/US 98/15096

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 98/15096

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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